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NOVARTIS
ONCOLOGY

August 22 , 2002

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20857

Re: Docket 01P-0574/CP1

To whom it may concern:

Novartis Pharmaceuticals Corporation ("Novartis") provides this response to the most recent comments of Ben Venue Laboratories, Inc. ("Ben Venue"), which were logged in at FDA on July 19, 2002[1] and submitted in support of the citizen petition assigned to the docket referenced above. In all of Ben Venue's communications regarding this petition, its primary focus has been the pursuit of FDA approval to commercialize an outdated and less safe formulation of Sandostatin® (octreotide acetate) Injection. At this juncture, as in our earlier submissions, Novartis seeks to restore focus on the appropriate scientific and regulatory issues surrounding the development and approval of the current Sandostatin Injection product and clarify the issues that, according to the regulations, should ensure that patients are not treated with the Sandostatin formulation abandoned by Novartis when a safer alternative was approved and made available.

Novartis will respond to the issues in the order in which they appear in Ben Venue's letter.

The New Formulation Of Sandostatin Is A Safer Formulation

Novartis not only claims, but has demonstrated in a blinded clinical study,[2] that the formulation for which Ben Venue is seeking approval is less safe than the currently approved formulation. Since the design and goals of that study apparently are a source of confusion, following is a clarification of the points raised by Ben Venue:

01P-0574 RC4

[1] The actual date of the letter is not visible on the docketed copy.

[2] The study report was submitted to FDA in July 1993. A copy of that report ("Bioequivalence Study of the Two Preparations of SMS 201-995"', Sandoz Pharmaceuticals Ltd., Tokyo, Japan, March 1988) was included in Novartis' submission to this docket on February 14, 2002.

1) "Elimination" of Local Pain

As Ben Venue asserts, Novartis did, indeed, seek "to eliminate the local pain" at the injection site through development of an improved formulation. Novartis did not, however, think it necessary to explain that the pain we sought to eliminate was that associated with the *product itself* and not with its physical administration by injection.[3] To the extent that the absence of this explanation has been a source of confusion, let us clarify now that the reduction of the pain attributable to the octreotide acetate preparation due to the acetic acid buffer system was precisely what was sought and achieved in Novartis' reformulation efforts.

2) Increased Safety and Reduced Pain Has Been Demonstrated Clinically With the Currently-Approved Formulation

In a last ditch effort to achieve its commercial objectives, Ben Venue has attempted to cast a false and confusing light on the study Novartis submitted to FDA to obtain approval of the improved (lactic acid buffer system) formulation. Briefly, Ben Venue's argument centers around the fact that subjects in the bioequivalence trial reported "mild" pain at the injection sites of the old (acetic acid buffer system) formulation.[4]

Novartis had two goals for this single-dose, blinded, crossover bioequivalence study: to provide concrete data to demonstrate bioequivalence of the two formulations, and to show the difference in safety between them. The design (including the number of subjects) was, and currently is, a common one for a bioequivalence demonstration: 16 healthy male volunteers were dosed and plasma levels were tested with one formulation, a washout period intervened, and then dosing/testing with the other formulation was completed. In selecting the dose to be tested, Novartis' goal was to produce measurable drug plasma levels while exposing study subjects to the least risk practically possible. Therefore, the *minimal* dose of 100mcg Sandostatin Injection was chosen for study. However, even at this level, 9 of the 16 subjects reported mild pain after only a single injection of the formulation with the outdated acetic acid buffer system. Only 1 subject reported pain after injection of the new/current (lactic acid) formulation.

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[3] Novartis expects that it is obvious that the technology to make any injection completely painless does not currently exist. Accordingly, Novartis did not explain this point.

[4] This study was submitted to FDA in what was hoped to be sufficient time to be approved simultaneously with the supplemental NDA for the acromegaly indication. Manufacturing site inspection scheduling issues with FDA prevented this.

The Pharmaceutical Expert Report (an excerpt of which was appended to Novartis' May 3, 2002, letter to this docket) provided the answer to why the change in components of the buffer system (i.e., from acetic acid to lactic acid) reduced the incidence of pain:

> "... the physiological pH of about 7.2 at the injection site is more rapidly re-established after injection of lactic acid than after injection of acetic acid. Lactic acid (pK 3.86) has a lower buffer capacity than acetic acid (pK 4.76) at pH 4.2[5] (lactic acid is partially neutralised with sodium hydrogen carbonate to pH 4.2, acetic acid is buffered to pH 4.2 by sodium acetate)." [6]

Ben Venue has erroneously concluded that "there are essentially no safety concerns regarding pain at the injection site" because there were no dropouts caused by injection site pain or reports of moderate or severe pain during the single-dose, crossover clinical trial. In advancing this assertion, Ben Venue disregards the manner in which patients with acromegaly, carcinoid syndrome, or VIPomas (the labeled indications of Sandostatin Injection) are treated. It is essential to understand that these patient populations require *between three and fifteen times* the dose tested in the bioequivalence study and, even more significantly, that the drug must be administered to these patients in 2 - 4 divided doses *daily for the rest of their lives*. In the study, neither the dose level (minimal) nor the dose frequency (once) were selected to mimic the significantly greater exposure experienced in patients' real-life situation.

The study confirmed the pharmaceutical experts' scientific conclusion that occurrence of the pain turns on which buffer system is used in the drug preparation. It is logical, therefore, to expect even greater pain at the injection site when the outdated formulation is used at the higher doses necessary for effective relief of symptoms. In the face of these data, Ben Venue's unsubstantiated claim – that cost will influence compliance more than the unnecessary pain inflicted by dosing with an outdated formulation – does not demonstrate adequate regard to the individual patients disease management strategy.

In its attempt to disparage the study design and gain approval to sell the more painful formulation, Ben Venue has lost sight of the needs of the very populations it purportedly

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[5] The pH of Sandostatin® (octreotide acetate) Injection is 4.2.

[6] "Sandostatin® Ampoules 0.1mg/1ml (Lactic Acid/Mannitol Formulation), Part 1 C: Expert Report on 1. Chemical and Pharmaceutical Documentation", Sandoz Ltd., Basle, Switzerland, 36/40Dr. DS, June 14, 1989, at Format 2a. A substantially identical volume was prepared in connection with the 0.5mg/mL product.

seeks to treat. Moreover, while they have erroneously attributed Novartis' reformulation activities to "economic considerations and not safety or efficacy", it is Ben Venue's intention to market the more painful formulation that shows a self-serving, financial motivation.

Finally, with regard to the intravenous use of the outdated formulation, Ben Venue makes the assertion that the increased safety shown by the lactic acid formulation given subcutaneously will not be seen when the drug is administered by vein. This position is unsupported by any data, including the bioequivalence study previously cited, Because of our experience with the approved and labeled indications for this product, Novartis would welcome the opportunity to provide advice on the design of any clinical study of intravenous dosing that Ben Venue or others might wish to conduct in order to prove their contention. Absent submission to this docket of such proof from an appropriately designed study, Ben Venue's contention merits no consideration by the Agency.

The Regulations Do Not Permit The Formulation Changes Ben Venue Seeks to Reintroduce In Their Generic Octreotide Acetate Product

Since the first indications for Sandostatin Injection were approved by FDA in 1988, there has been an open and ongoing dialogue between Novartis and the Agency regarding this important product. FDA has been involved in all decisions bearing on the availability of Sandostatin Injection and has the most complete picture of its development and improvement over time. This does not alter the reality that the regulations overarch the activities of FDA and sponsors alike. These regulations, binding anyone filing or evaluating an abbreviated new drug application ("ANDA"), are abundantly clear.

Ben Venue correctly contends that they are permitted, under 21 CFR 314.94(a)(9)(iii), to seek approval for a parenteral product that has a different buffer from the innovator. However, they continue to neglect to complete the thought codified in that section:

> "...an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that *the differences do not affect the safety of the proposed drug product.*" 21 C.F.R. § 314.94(a)(9)(iii) (emphasis at end added).

Vis-à-vis formulation differences, 21 C.F.R. § 314.127(8)(ii)(B) also provides no support for the reinstatement of a formulation abandoned for safety reasons:

> "FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the abbreviated new drug application unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, *if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety of the drug product."* (emphasis added)

With respect to any waiver of in vivo bioequivalence testing requirements, Ben Venue's contention that "FDA has a long history of waiving in vivo bioequivalence requirements for ANDAs seeking approval of parenteral drug products that differ in preservative, buffer system, substances to adjust pH" reflects a basic misapplication of the codified regulations. Again, an ANDA sponsor can change the buffer in and "seek approval of" its product if it can demonstrate that such a difference has no safety consequences. 21 C.F.R. § 314.94(a)(9)(iii). However, in "seek[ing] approval of" such a modified product, the sponsor is ineligible for a bioequivalence waiver because its product does not "contain[] the same active and inactive ingredients in the same concentration" as the RLD. 21 C.F.R. § 320.22(b)(1). Moreover, in situations such as this one where there is a demonstration of an effect on safety of the drug product, section 314.94 requires FDA to reach a different conclusion than the one advanced by Bedford. Indeed, in this case, FDA need not "predict the consequences of minor changes," because it already has a clinical study that demonstrates the negative safety consequences should the contested change be permitted.

Ben Venue protests that were it not for the use of a different tonicity agent[7] in their proposed ANDA formulation, no one, including Novartis, would have had the opportunity to participate in this public proceeding regarding their attempt to obtain FDA approval to sell an inferior formulation at a somewhat reduced price to an unsuspecting public. Novartis devoutly hopes this is not true. In fact, the regulations cited above are specifically drafted to prevent the marketing of such a product.

Finally, Ben Venue's "curiosity" about the timing of the discussion in Novartis' submissions on the safety of the old Sandostatin formulation is easily dispatched: Novartis only joined this discussion when it was revealed (through Ben Venue's filing of its citizen petition) that a proposal for the return of the more painful formulation to the marketplace was being considered. As detailed above, the regulations state that no

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[7] The reference listed drug ("RLD") uses mannitol, while the tonicity agent used in the formulation proposed in the ANDA Ben Venue seeks to file would be sodium chloride.

ANDA-based product may contain any active or inactive ingredient that compromises the safety of the innovator drug product/RLD. Because the use of an acetic acid buffer system has been demonstrated clinically to be less safe than the current formulation, it cannot be construed that "the difference does not affect the safety of the drug product." In accordance with 21 C.F.R. § 314.94(a)(9)(iii) and 21 C.F.R. § 314.127(8)(ii)(B), an ANDA for such a product cannot be approved, and the filing of an ANDA for such a product as Ben Venue seeks here should not be permitted.

Novartis/Sandoz Worked With FDA To Bring The Improved Formulation To Its Patients

The aspersions Ben Venue casts as to the need for, and the timing of, the Sandostatin Injection re-formulation are self-serving and meritless. Novartis confirmed, in healthy subjects at the lowest possible dose that would address the issue, that injection site pain was both real and remediable. The demonstrably safer formulation was submitted to FDA in July 1993 – a timeframe that was expected (and hoped) would permit its approval simultaneously with that of the supplemental NDA for the most significant of its three labeled indications (acromegaly). As noted previously, FDA's overwhelming schedule of manufacturing site inspections during its review of the supplemental NDA following its July 1993 submission prevented this from happening. Now that the safer formulation has completely replaced the older version, there is no excuse to re-expose patients to the pain that Novartis' early pharmacovigilance eliminated.

Ben Venue's most recent comments insinuate that Novartis' motivation in 1993 to replace the acetic acid formulation was not related to the relative safety of the formulations, but instead was motivated by the intellectual property protection that applies to the improved lactic acid product. However, separate and apart from this administrative proceeding, Ben Venue (through its affiliated company, Bedford Laboratories) provided Novartis with notice of a Paragraph IV Patent Certification that was filed earlier this year in connection with a pending ANDA for its alternative octreotide product, which is buffered with lactic acid. Based upon the representations in that Certification, Novartis elected not to initiate patent infringement litigation.[8] Accordingly, the scenario spun by Ben Venue in its most recent submission to this docket bears no relation to the situation at hand. The facts surrounding the

[8] Novartis knows nothing more about the product that is the subject of the Ben Venue/Bedford ANDA than what was represented in the notice of the Paragraph IV Patent Certification. Should the product approved by FDA or marketed by Ben Venue/Bedford differ in any respect from the product described in that Certification, Novartis will proceed accordingly based upon an evaluation of that product and Novartis' patent claims.

reformulation of Sandostatin Injection in 1993 show that Novartis heard the input of its patient populations, developed a safer formulation, and accessed the appropriate channels and authorities to make that improved formulation available to the public.

* * *

Novartis hopes that the above information will further elucidate the issues surrounding the development and approval of the current Sandostatin (octreotide acetate) Injection product and assist FDA in addressing the citizen petition. Please feel free to contact the undersigned, at (973) 781-8697, if there are any questions or if additional information is required.

Respectfully submitted,

Robyn B. Konecne, Pharm. D.

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Associate Director
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cc: Mr. Gary J. Buehler, Director, Office of Generic Drugs (HFD-600)
David Orloff, M.D., Dir., Div. of Metabolic and Endocrine Drug Prods. (HFD-510)

170

252

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447